

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

09/865,071

AL

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 487/14, A61K 31/495 // (C07D 487/14, 239:00, 249:00, 249:00) (C07D 487/14, 231:00, 239:00, 249:00)		A1	(11) International Publication Number: WO 95/01356 (43) International Publication Date: 12 January 1995 (12.01.95)
(21) International Application Number: PCT/EP94/02031 (22) International Filing Date: 22 June 1994 (22.06.94)			(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(30) Priority Data: MI93A001396 29 June 1993 (29.06.93)		IT	
(71) Applicant (for all designated States except US): SCHERING-PLOUGH S.p.A. [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): BARALDI, Pier, Giovanni [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). ZAPPA-TERRA, Laura [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). ONGINI, Emanio [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). (74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevetuale, Via Rossini, 8, I-20122 Milano (IT).			Published With international search report.
(54) Title: 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A ₂ RECEPTOR			
(57) Abstract The compounds of formula (I) wherein R and A have the meanings given in the specification, are endowed with selective A ₂ adenosine receptor antagonistic activity.			
<p style="text-align: right;">(I)</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NB	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
RJ	Bosnia	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	L1	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES
HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A₂ RECEPTOR

The present invention relates to compounds having antagonistic activity on adenosine A₂ receptor.

Adenosine is known to modulate a number of physiological functions. At the cardiovascular system level, 5 adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a diphasic action, 10 inducing vasoconstriction at low concentrations and vasodilatation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T.W., Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291-429; Progress Cardiovasc. Dis. 1989, 32, 73-97).

A number of studies showed adenosine actions are mediated by two subtypes of receptors which are located on the cell membrane: an high-affinity one, inhibiting 20 the activity of the enzyme adenylate cyclase (A₁ receptor), and a low-affinity one, stimulating the activity of the same enzyme (A₂ receptor) (J. Med. Chem. 1982, 25, 197-207. Physiol. Rev. 1990, 70(3), 761-845. J. Med. Chem. 1992, 35, 407-422).

25 Intense research efforts have made it possible to identify and develop analogs to adenosine able to interact as agonists with the A₁ and A₂ receptor. As far as the antagonists are concerned, it is known that some

compounds with a xanthine structure are selective antagonists for the A₁ receptor.

(J. Med. Chem., 1992, 25, 407-422). New compounds of pharmacological interest which possess an high antagonistic action for the A₂ receptor have not yet been found.

The knowledge available on the physiological role of adenosine and its involvement in some pathological processes suggests that selective antagonists for the A₂ receptor can be of pharmacological interest. At the level of the central nervous system, antagonistic A₂ compounds should stimulate various cerebral functions and so possess antidepressive and stimulating properties for the cognitive functions. Moreover, numerous data show that the A₂ receptors are present in high density in the basal ganglia of which the importance in the control of movement is known. Hence the hypothesis that A₂ antagonists can improve motor-deficiency due to neurodegenerative processes at the level of important cerebral nuclei. It follows that A₂ receptor antagonists could be useful in the treatment of neurodegenerative pathologies. Amongst these are included Parkinson's disease, senile dementia as in Alzheimer's disease and psychosis of an organic origin (Drug Dev. Res., 1993, 28, 381-385).

At a peripheric level, A₂ receptor antagonists could stimulate the respiratory functions and therefore have a therapeutic effect in the treatment of bronchospasm and more generally asthma. Moreover, with regard to the effects at a cardiovascular or renal level, an advantageous activity on renal flow can be envisaged

and therefore the possibility of the treatment of renal insufficiency and of various cardiovascular disturbances.

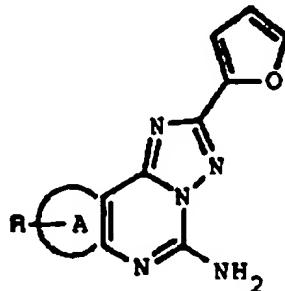
Some reference compounds interacting with A₂ receptor, even though in a not selective way, are known.

5 5-Amino-9-chloro-2(2-furyl)1,2,4-triazolo[1,5-c]quinazoline, named CGS 15943 (J. Med. Chem., 1988, 31, 1014-1020) and 4-amino-8-chloro-1-phenyl(1,2,4)-triazolo(4,3-a)quinoxaline, named CP 66,713 (J. Med. 10 Chem., 1990, 33, 2240-2254) are compounds having a good affinity for A₂ receptor, but also active on A₁ receptor. Only recently, xanthine derivatives have been found, e.g. (E)-1,3-dialkyl-7-methyl-8-(3,4,5-trimethoxystyryl)xanthines (J. Med. Chem., 1992, 35, 2342-15 2345), which seem to have a selective antagonistic activity on A₂ receptors. However, the pharmacological profile thereof is unknown.

The compounds of the invention have the following general formula I:

20

25



I

in which:

A is a pyrazole, imidazole or triazole ring;

30 R is hydrogen; C₁-C₈ alkyl; C₃-C₇ alkenyl, C₃-C₇ alkynyl; C₃-C₇ cycloalkyl; C₁-C₅ alkyl substituted with

one or more halogen atoms, hydroxy groups, C₁-C₄ alkoxy, C₃-C₇ cycloalkyl, groups of formula -NR₁R₂, -CONR₁R₂; aryl optionally substituted with halogen atoms, C₁-C₄ alkoxy groups, C₁-C₄ alkyl, nitro, amino, 5 cyano, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, carboxy, carboxyamido; C₇-C₁₀ aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a group of formula -(CH₂)_m-Het, wherein Het is a 5-6 membered aromatic or 10 non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer from 1 to 5;

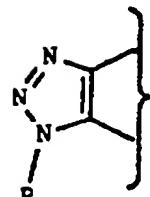
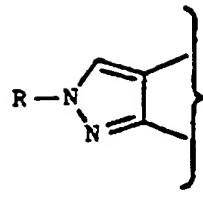
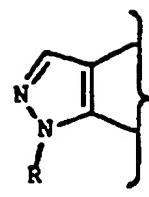
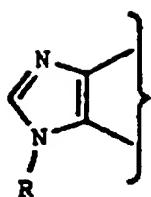
R₁, R₂ which are the same or different, are hydrogen, C₁-C₅ alkyl, C₇-C₁₀ aralkyl, phenyl, or taken together 15 with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring containing one or more heteroatoms such as N, O, S and n is an integer from 2 to 5, with the proviso that, when A is a pyrazole or imidazole, R is different from 20 fluorobenzyl.

The disclaimed compounds are disclosed in Eur. J. Med. Chem., 1993, 28, 569-576,

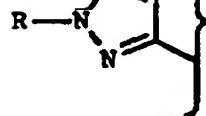
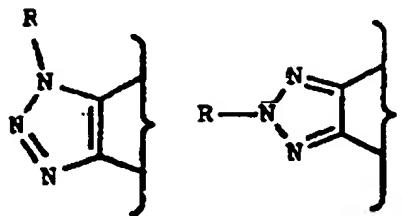
The invention also comprises the pharmaceutically acceptable salts of the compounds of general formula I.

25 The possible meanings of A can be represented by the following structural formulae:

5



5



In compounds of formula I, examples of C₁-C₈ alkyl groups comprise preferably methyl, butyl and isopentyl.

Examples of C₃-C₇ cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl.

Examples of C₁-C₅ alkyl groups substituted with C₃-C₇ cycloalkyl groups are cyclohexylmethyl, cyclopentylmethyl, 2-cyclopentylethyl.

Examples of substituted C₁-C₅ alkyl groups comprise 2-hydroxyethyl, 2-methoxyethyl, trifluoromethyl, 2-fluoroethyl, 2-chloroethyl, 3-aminopropyl, 2-(4-methyl-1-piperazine)ethyl, 2-(4-morpholinyl)ethyl, 2-aminocarbonylethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl. Aryl is preferably phenyl, optionally substituted with chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups. Examples of 5-6 membered heterocyclic groups containing N, O, S comprise piperazinyl, morpholinyl, thiazolyl, pyrazolyl, pyridyl, furyl, thieryl, pirrolyl, triazolyl, tetrazolyl. Examples of C₇-C₁₀ aralkyl groups comprise benzyl or phenetyl optionally substituted by one or more substituents selected from chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups.

Preferably, R is hydrogen, C₁-C₈ alkyl, aryl or C₇-C₁₀ aralkyl optionally substituted, preferably with halogen atoms.

Particularly preferred compounds I are those in which R is a phenetyl group in which the phenyl ring may optionally be substituted by one or more substituents selected from chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups.

The compounds of general formula I have advantageous biochemical and functional properties related to their antagonistic action on the A₂ adenosine receptor, compared with the reference compounds CGS 15943 and (5-amino-8-(4-fluorobenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine), disclosed in Eur. J. Med. Chem., 1993, 28, 569-576 and hereinafter referred to as 8FB-PTP. The effects of the disclosed A₂ receptor antagonists may be demonstrated in one or more of the following standard in vitro and/or in vivo tests.

IN VITRO TESTS

Receptor binding

This test involves the ability of adenosine antagonists to displace radiolabeled agonists from A₁ and A₂ adenosine binding sites in membrane preparations from rat brain.

The rat cerebral tissue (whole brain and striatum) was from male Sprague-Dawley rats weighing 150-200 g. A₁ and A₂ receptor binding assays were performed according to Bruns et al. (Proc. Natl. Acad. Sci. U.S.A., 1980, 77, 5547-5551) and Jarvis et al. (J.

Pharmacol. Exp. Ther., 1989, 251, 888-893), using [3H]N6-cyclohexyladenosine ([3H]CHA) and [3H]2-[p-(2-carboxy ethyl)-phenethylamino]-5'-N-ethylcarboxamido-adenosine ([3H]CGS 21680) as radioligands,
5 respectively.

The test compounds were dissolved in dimethylsulphoxide (DMSO) and then diluted with assay buffer to give the test solutions. The final concentration of DMSO did not exceed 1% by volume, at
10 which level it did not affect radio ligand binding to the membrane receptor.

The selectivity for A₂ receptors was evaluated by comparing the affinities of each compound for A₁ and A₂ receptors. A marked relationship between binding
15 affinities and physiological effects modulated by adenosine receptors has been demonstrated elsewhere (Conti et al., Naunyn-Schmied. Arch. Pharmacol., 1993, 348, 108-112).

The disclosed compounds, described in formula I,
20 have marked A₂ receptor affinity with K_i values ranging from 1 nM to 100 nM (Table). Moreover, some compounds show A₂ versus A₁ selectivity higher than that of the reference compounds CGS 15943 and 8FB-PTP. In particular, compound 341 has a selectivity for A₂
25 versus A₁ receptors of about 50-fold.

Rat aorta and bovine coronary artery

The A₂ adenosine antagonistic activity of these compounds was investigated by evaluating their ability to counteract vasodilation induced by adenosine
30 agonists in vascular tissues, such as rat aorta and bovine coronary arteries, after precontraction with 3μM

of prostaglandin F₂ α . The method used to test adenosine agonists is described elsewhere (Conti et al., Naunyn-Schmied. Arch. Pharmacol., 1993, 348, 108-112). Cumulative dose-response curves were constructed, 5 using increasing concentration of NECA (1 nM-10 μ M), in the absence or presence of the antagonist.

Many of the test compounds, at concentrations ranging from 0.03 to 1 μ M, were able to shift to the right the dose-response curves of the agonist in a 10 concentration-dependent manner.

Rat atria

The ability of the disclosed compounds to antagonize the negative chronotropic effect induced by A₁ receptor agonists was tested on isolated rat atria, 15 whose beating rate is known to be modulated by A₁ adenosine receptors. The method used to test adenosine agonists is described elsewhere (Conti et al., Naunyn-Schmied. Arch. Pharmacol., 1993, 348, 108-112). The decrease in atrial rate evoked by cumulative 20 addition of the A₁ selective agonist, 2-chloro-N⁶-cyclopentyladenosine (CCPA) was measured. The dose-response curves of the agonist was then repeated in the presence of the antagonist. The receptor selectivity of test compounds can be evaluated by comparing the 25 activities of each compound in antagonizing either A₂ (vasodilation)- or A₁ (heart rate)-mediated responses.

Some of the disclosed compounds were found to have little or no effects on the A₁-mediated response in 30 isolated rat atria. In particular, compound 341 is ineffective in this functional model, thus confirming

its A₂ versus A₁ selectivity observed from binding studies.

IN VIVO TESTS

Behavioral effects

5 The behavioral response to treatment with different doses (ranging from 1 to 100 mg/Kg) of the test compounds administered parenterally were evaluated in Swiss mice using the classic "Irwin test" (Irwin, Psychopharmacologia, 1968 13, 222-257). Behavior, 10 autonomic and neurological functions of the animals were assessed through 36 different parameters evaluated during observation sessions at 1, 2, 4 and 6 h after drug administration. The animals were observed until 24 h after administration for checking mortality.

15 The test compounds produced no mortality and only tended to stimulate central nervous system activity.

Hemodynamic tests

20 In adult male spontaneously hypertensive rats, some of the disclosed compounds were administered parenterally at increasing doses (1-30 mg/Kg) and their ability in antagonizing the bradycardic and hypotensive effects induced by A₁ and A₂ adenosine receptor agonists, respectively, was measured. Systolic blood pressure and heart rate were measured in conscious 25 animals by the tail-cuff method as described elsewhere (Monopoli et al., Arch. Int. Pharmacodyn. Ther., 1987, 286, 246-254).

30 The test compounds antagonize hypotension induced by A₂ agonists with a potency similar or higher than that of the reference compounds CGS 15943 and 8FB-PTP, whereas some of them antagonize the

A_1 -mediated responses slightly and only at higher doses.

TABLE - BIOLOGICAL ACTIVITY OF A SERIES OF NEW A2 ADENOSINE RECEPTOR ANTAGONISTS

5

	Compound N°	Binding ^a		Selectivity A_1/A_2
		A_1 Ki (nM)	A_2	
10	DCPCX	1.5	727	0.002
	CGS 15943	6.4	1.2	5.3
	8FB-PTP	3.3	1.2	2.8
	N° 292	237	9.0	26.3
	N° 294	31.2	2.4	13.0
15	N° SP 319	120	12.6	9.5
	N° SP 320	5.8	1.9	3.1
	N° SP 340	61.5	13.8	4.4
	N° SP 341	123	2.4	51.3
	N° SP 363	18.6	2.6	7.2
20	N° SP 375	4.7	1.5	3.2
	N° SP 376	42.6	7.1	6.0

^aInhibition of [³H]CHA binding (A_1) in rat whole brain homogenates or [³H]CGS 21680 binding (A_2) in rat striatal homogenates.

25

- DPCPX (8-cyclopentyl-1,3-dipropylxanthine) is a standard A_1 selective antagonist (Bruns et al., Naunyn-Schmied. Arch. Pharmacol., 1987, 335, 59-63).

30

- CGS 15943 (5-amino-9-chloro-2-(2-furyl)1,2,4-triazolo[1,5-c]quinazoline is a reference slightly selective A2 antagonist (Francis et al., 1988, J.

Med. Chem., 31, 1014-1020).

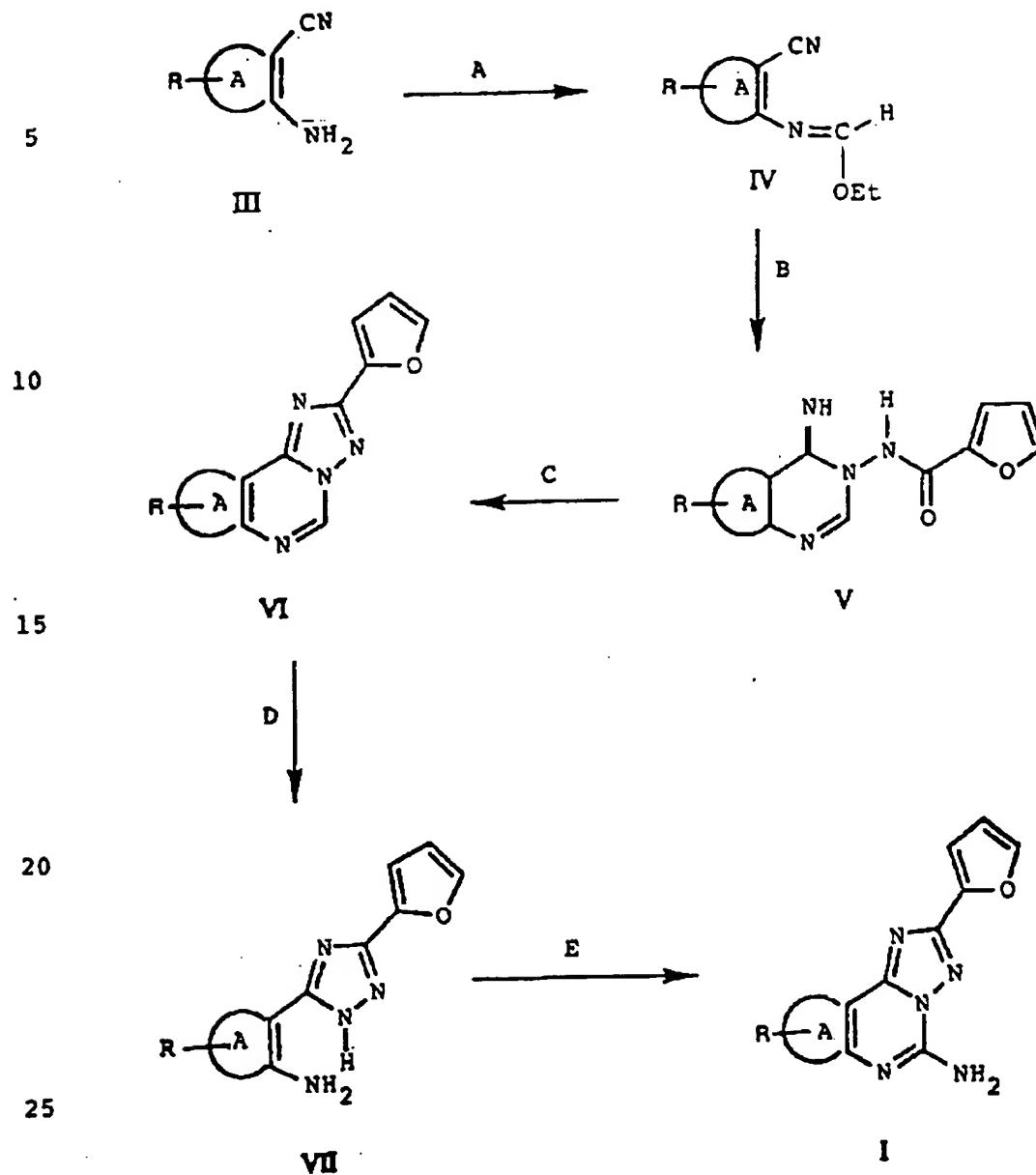
- 8FB-PTP (5-amino-8-(4-fluorobenzyl)-2-(2-furyl)-
pyrazolo[4,3-4e]-1,2,4-triazolo[1,5-c]pyrimidine)
is a reference slightly selective A2 antagonist
5 (Gattà et al., Eur. J. Med. Chem., 1993, 28, 569-
576).

For the envisaged therapeutical uses, compounds I
will be formulated as suitable pharmaceutical composi-
tions, which can be administered, for example, by the
10 oral, parenteral or transdermal routes, using known
techniques and excipients, as described for example in
Remington's Pharmaceutical Sciences Handbook, Mack Pub.
Co., NY, USA, XVII ed. The daily dosage will depend, of
course, on many factors (severity of the pathology to
15 treat, patient conditions, toxicology and pharmacokine-
tic of the selected compound) but generally it will
range from 0,01 to 10 mg/kg body weight, preferably
from 0,1 to 1 mg/kg, optionally subdivided in more ad-
ministrations. Examples of pharmaceutical compositions
20 comprise capsules, tablets, solutions, syrups, vials,
controlled-release forms, transdermal forms (cerotti)
and the like.

The compounds of the invention were prepared ac-
cording to the synthetic schemes reported below.

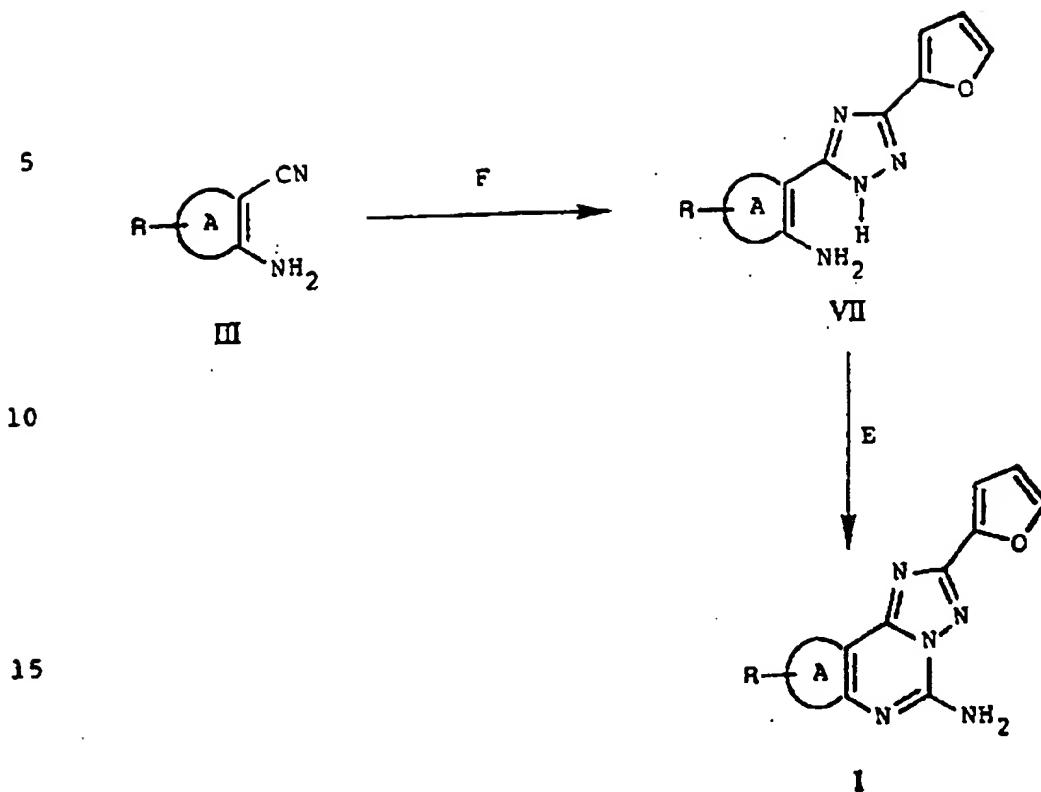
12

Scheme I



Reagents: A) triethyl orthoformate; B) 2-furoic acid hydrazide, 2-methoxyethanol; C) PhOPh, 260°C; D) 10% HCl, under reflux; E) cyanamide, pTsOH, N-methylpyrrolidone

Scheme II



20 Reagents: F) furoic acid hydrazide, diphenylether; E)
cyanamide, pTsOH, N-methylpyrrolidone.

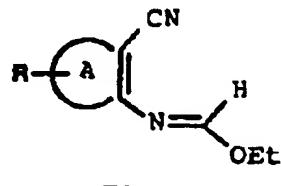
The compounds of formula I of the invention can be prepared through either an indirect route described in Scheme I or a direct route described in Scheme II.

25 Suitable starting materials for both schemes are
the heterocyclic ortho-amino nitriles of formula III,
generally prepared according to synthetic procedures
known in literature and reported in the book by
E.C.Taylor and A.McKillop (vol. 7 of the series Advan-
30 ces in Organic Chemistry, Ed. Interscience, 1970).

14



Ortho-amino nitriles III are transformed into the corresponding imidates of formula IV by reaction with an ethyl orthoformate excess at the reflux temperature for 8-10h. The reaction, after evaporation of the ethyl orthoformate, leads to the substantially pure corresponding imidates IV in a high yield as evidenced by the IR and ^1H NMR analysis on the crude reaction products.

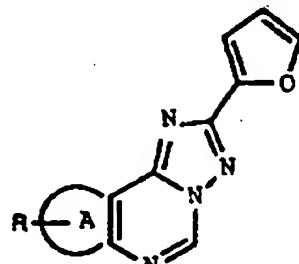


15

IV

The imidates of formula IV are then subjected to a sequence of two reactions allowing to obtain the tricyclic structures of formula VI in a high yield.

20



25

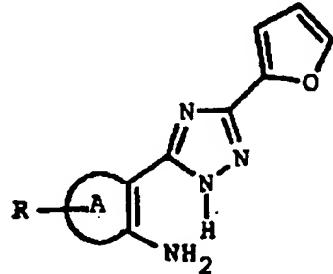
VI

The reaction sequence comprises: a) reaction with 2-furoic acid hydrazide in a 2-methoxyethanol solution at the reflux temperature for 8-10h, to obtain the intermediates compounds of formula V; b) thermal cyclization of the latter to corresponding compounds of for-

mula VI, by heating in diphenyl ether at the temperature of 260°C for 0.5-1h.

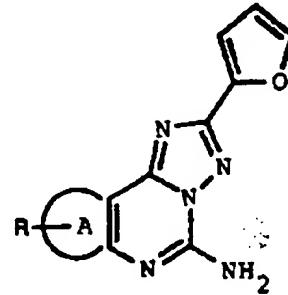
The tricyclic compounds VI are then hydrolyzed with 10% HCl at the reflux temperature for 1-3h to give 5 triazoles VII, which are finally cyclized to desired compounds I with cyanamide in N-methyl pyrrolidone at the reflux temperature and in the presence of para-toluenesulfonic acid (Scheme I).

10



15

VII



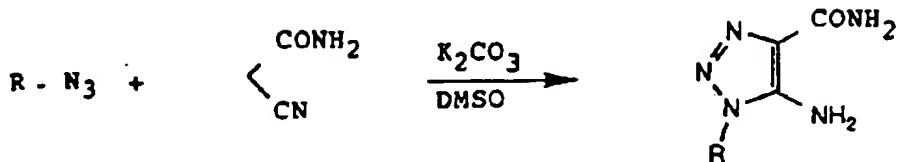
I

In some cases, triazoles VII can be obtained directly heating in diphenyl ether ortho-amino nitriles III with 2-furoic acid hydrazide. Triazoles VII are 20 then cyclized as described above (Scheme II). In the following schemes III, IV and V, the synthesis of the compounds I in which A is a triazole ring is reported in more detail.

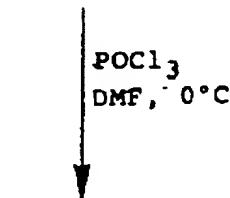
Scheme III

Synthesis of 5-amino-7-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives

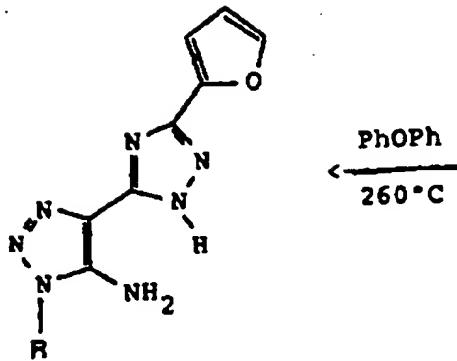
5



10



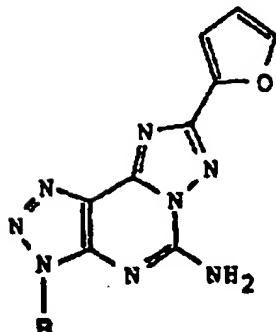
15



20

$\text{NH}_2\text{-CN}$
 $pTs\text{-OH}$
 $N\text{-methylpyrrolidone, } 160^\circ\text{C}$

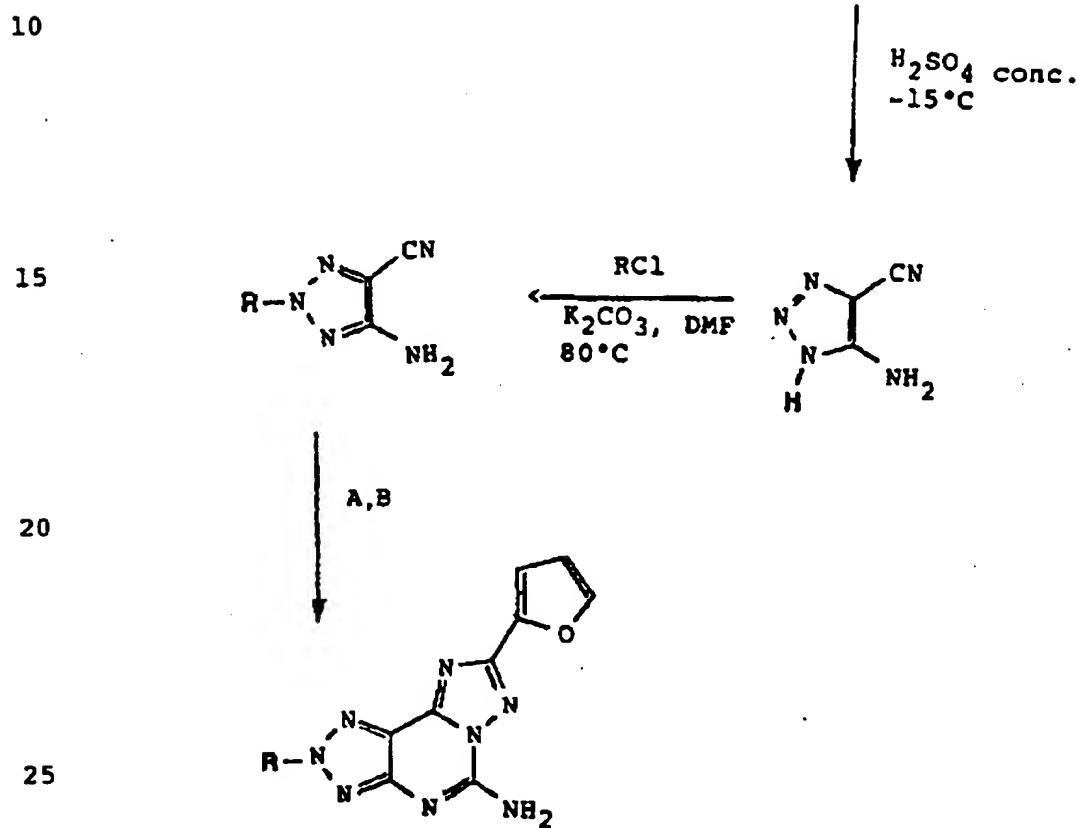
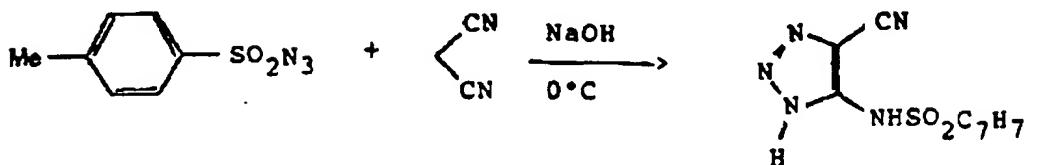
25



30

Scheme IV

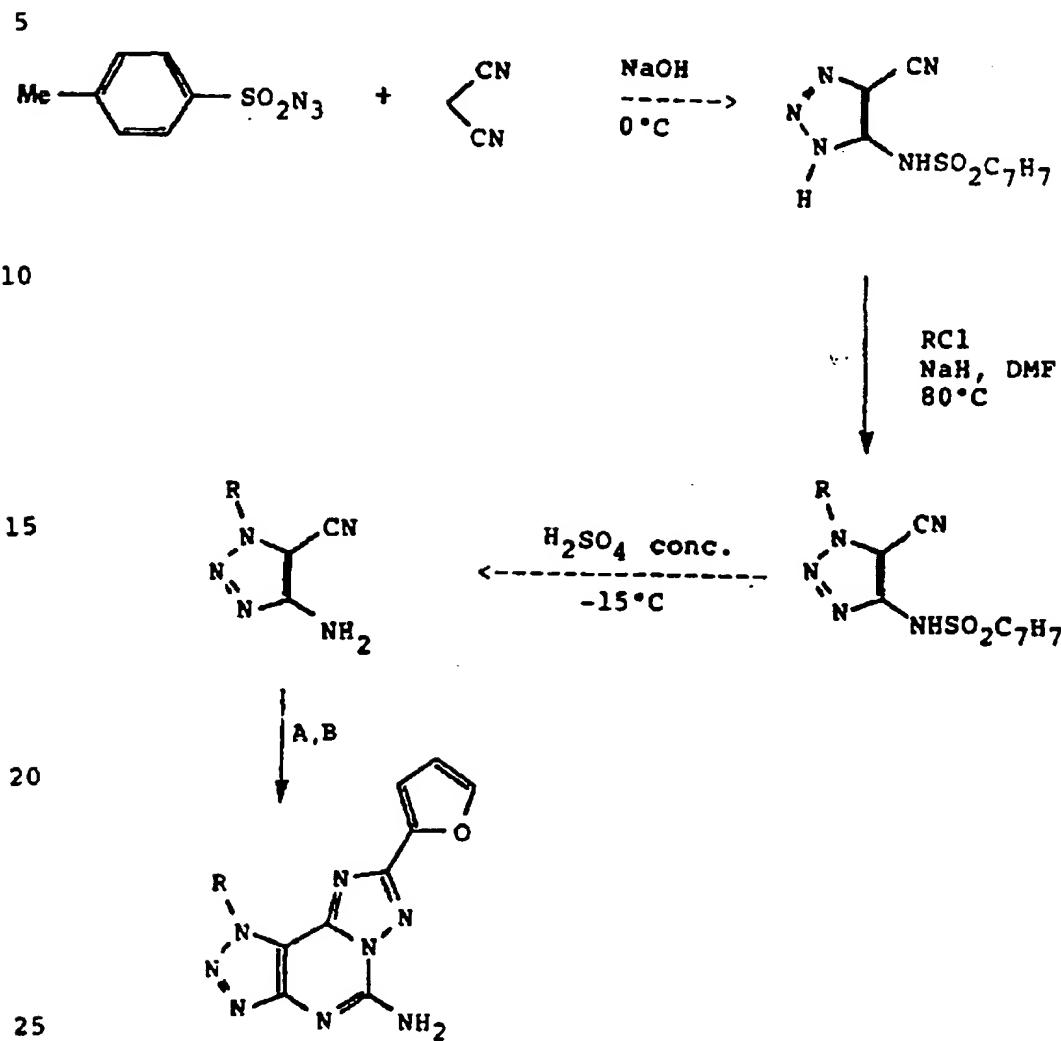
Synthesis of 5-amino-8-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives



30 Reagents: A) furoic acid hydrazide, PhOPh, 260°C, B)
NH₂CN, pTsOH, N-methylpyrrolidone.

Scheme V

Synthesis of 5-amino-9-substituted-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine derivatives



30 Reagents: A) furoic acid hydrazide, PhOPh, 260°C, B)
 NH_2CN , pTsOH, N-methylpyrrolidone.

The following examples illustrate the invention in more detail.

Example 1

According to the procedures described in J. Org. Chem. 1956, 21, 1240; J. Am. Chem. Soc. 1956, 78, 784 and the references herein cited, the following compounds are prepared, starting from commercially available ethoxy-methylene malondinitrile and N1-substituted hydrazines, which also are mainly commercially available:

1-methyl-4-cyano-5-aminopyrazole
1-n-butyl-4-cyano-5-aminopyrazole
1-isopentyl-4-cyano-5-aminopyrazole
1-(2-cyclopentyl)ethyl-4-cyano-5-aminopyrazole
1-hydroxyethyl-4-cyano-5-aminopyrazole
1-phenyl-4-cyano-5-aminopyrazole
1-tert-butyl-4-cyano-5-aminopyrazole
1-phenylethyl-4-cyano-5-aminopyrazole
1-(2-chlorophenyl)-4-cyano-5-aminopyrazole.

Example 2

Starting from 4-cyano-5-aminopyrazole, prepared according the procedure reported in Chem. Pharm. Bull. 1970, 18, 2353 or in J. Heterocyclic Chem. 1979, 16, 1113, 1-substituted 4-cyano-3-aminopyrazoles can be prepared by direct alkylation with the corresponding alkyl halide in dimethylformamide at 80°C for 1-2h in the presence of anhydrous potassium carbonate. From the reaction mixture, containing the two N₁ and N₂ alkylated position isomers in an about 1:2 ratio, the N₂ isomer can be isolated by a single crystallization or column chromatography on silica gel eluting with

ethyl acetate and petroleum ether mixtures. Using said procedures, the following compounds were prepared:

1-methyl-4-cyano-3-aminopyrazole
1-butyl-4-cyano-3-aminopyrazole
5 1-benzyl-4-cyano-3-aminopyrazole
1-isopentyl-4-cyano-3-aminopyrazole
1-phenylethyl-4-cyano-3-aminopyrazole

Example 3

a) A suspension of anhydrous potassium carbonate (30 mmols) in DMF (50 ml) is added with 3-amino-4-cyano-pyrazole (20 mmols), heating to a temperature of 80°C for 30 minutes. The suspension is added with phenethyl bromide (25 mmols) and is heated to 80°C for 2h. After cooling to room temperature, the mixture is evaporated to dryness under vacuum and the resulting residue is taken up with distilled water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts are dried over anhydrous sodium sulfate and evaporated to dryness under vacuum.

20 The resulting residue consists of a 1:3 mixture of 1-phenylethyl-4-cyano-5-aminopyrazole (20%) and of 1-phenylethyl-4-cyano-3-aminopyrazole (60%) which may be used as such in Example 4 or chromatographed on silica gel column eluting with an ethyl acetate/hexane mixture 25 to give:

1-phenylethyl-4-cyano-5-aminopyrazole m.p. 172-173°C;
(20%);
 $^1\text{H-NMR}$ (DMSO-d₆): 3.04 (t, 2H); 4.12 (t, 2H); 5.85 (sb, 2H); 7.21-7.30 (m, 5H); 7.41 (s, 1H); e 1-8-
30 phenylethyl-4-cyano-3-aminopyrazole m.p. 98-100°C
(60%); $^1\text{H-NMR}$ (CDCl₃): 3.07 (t, 2H); 4.10 (t, 2H); 4.23

(sb, 2H); 7.17 (s, 1H); 7.00-7.28 (m, 5H).

b) A solution of 1- β -phenylethyl-4-cyano-5-aminopyrazole (20 mmol) in triethylorthoformate (40 ml) is refluxed under nitrogen for 8 h.

The excess orthoformate is evaporated to dryness under vacuum and the residual yellow oil is dissolved in ethyl ether and percolated onto silica gel to give the corresponding iminoether (87% yield). The residue obtained after orthoformate evaporation is practically pure and is directly used in the following step. A solution of the iminoether (20 mmol) and of 2-furoic acid hydrazide (2.5 g, 22 mmol) in 2-methoxyethanol (50 ml) is refluxed for 5-10 h. After cooling, the solution is evaporated to dryness to give an oily residue which is subjected to thermal cyclization in diphenylether (50 ml) using a Dean-Stark apparatus so as to azeotropically remove water formed during the reaction. After 1.5 h, the reaction is checked in TLC (ethyl acetate:petroleum ether 2:1) and when the starting compound is completely absent, the mixture is cooled and added with hexane. The resulting precipitate is filtered and crystallized to give 7-(β -phenylethyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazole[1,5-c]pyrimidine m.p. 174-175°C (20%) 1H-NMR (DMSO-d₆): 3.23 (t, 2H); 4.74 (t, 2H); 6.75 (s, 1H); 7.14-7.17 (m, 5H); 7.28 (s, 1H); 7.98 (s, 1H); 8.53 (s, 1H); 9.56 (s, 1H).

In a similar way, starting from 1- β -phenylethyl-4-cyano-3-aminopyrazole, 8-(β -phenylethyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazole[1,5-c]pyrimidine m.p. 268-270°C (60%) 1H-NMR (DMSO-d₆): 3.32 (t, 2H); 4.72 (t, 2H); 6.73 (s, 1H), 7.23 (m, 5H); 7.95 (s, 1H); 8.8

(s, 1H); 9.41 (s, 1H) is obtained.

c) A suspension of a compound VI of step b) (10 mmol) in 10% HCl (5.0 ml) is refluxed under stirring for 3 h. After cooling, the solution is alkalinized with concentrated ammonium hydroxide at 0°C and the resulting precipitate is filtered or extracted with ethyl acetate (3 x 100 ml), dried and evaporated to dryness under vacuum, to give the corresponding 1-(β -phenylethyl)-4-[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-

pyrazole m.p. 175-176°C; $^1\text{H-NMR}$ (DMSO- d_6): 3.15 (t, 2H); 4.48 (t, 2H); 5.78 (s, 1H), 6.37 (s, 1H); 6.68 (s, 1H); 7.1 (s, 1H); 7.27-7.28 (m, 5H); 7.82 (s, 1H); 14.51 (sb, 2H); in a similar way 1-(β -phenylethyl)-4-[3(2-furyl)-1,2,4-triazol-5-yl]-3-aminopyrazole (m.p. 205-206°C); $^1\text{H-NMR}$ (DMSO- d_6): 3.12 (t, 2H); 4.46 (t, 2H); 5.75 (s, 1H); 14.41 (sb, 2H) is obtained.

d) Cyanamide (60 mmol) is added to a suspension of an amine of formula VII prepared in step c) (10 mmol) in N-methylpyrrolidone (40 ml) followed by p-toluensulfonic acid (15 mmol).

The mixture is heated to 160°C under stirring. After 4 h a second portion of cyanamide (60 mmol) is added and heating is continued overnight. The mixture is then treated with hot water (200 ml) and the precipitate is filtered, washed with water and crystallized from ethanol to give the corresponding 5-amino-7-(β -phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine m.p. 225-226°C $^1\text{H-NMR}$ (DMSO- d_6): 3.21 (t, 2H); 4.51 (t, 2H); 6.65 (s, 1H); 7.1-7.44 (m, 5H, arom and 1H); 7.78 (s, 1H); 7.89 (sb, 2H); 8.07 (s, 1H) (Compound 341); in a similar way 5-amino-8-(β -

phenylethyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazo-
le[1,5-c]pyrimidine m.p. 212-213°C ^1H -NMR (DMSO-d₆):
3.21 (t, 2H); 4.53 (t, 2H); 6.7 (s, 1H); 7.1-7.4 (m,
5H, arom and 1H); 7.65 (sb, 2H); 7.93 (s, 1H); 8.45 (s,
1H) (Compound 375) is obtained.

Example 4

A suspension of potassium carbonate (0.23 mole) in
DMSO (70 ml) is added subsequently with cyanoacetamide
(70 mmols) and p-fluorobenzylazide (54.5 mmols). The
10 resulting solution is stirred at room temperature for
1h and then poured into a large volume of water (1.5
l). The separated solid is filtered, washed with water
and dried in oven at 70°C to give 1(p-fluorobenzyl)-4-
carboxamido-5-amino-1,2,3-triazole (96% yield).

15 M.p.: 198-199°C; ^1H NMR (DMSO-d₆): 7.5-7.1 (m,6H); 6.4
(s,2H); 5.4 (s,2H).

An amide suspension (0.005 mole), stirred and coo-
led to 0°C, in DMF (5 ml) is added with phosphorous
oxychloride (0.01 mole). The resulting solution is
20 stirred for 5 minutes at 0°C, 10 minutes at 25°C and 15
minutes at 80°C. After cooling to room temperature, 5
ml of N HCl are added and the mixture is refluxed for 5
minutes. 1(p-Fluorobenzyl)-4-cyano-5-amino-1,2,3-tria-
zole separates from the cooled solution (90% yield).
25 M.p. 185-186°C; ^1H NMR (DMSO-d₆): 7.3-7.0 (m,6H); 5.5
(s,2H); IR (KBr) : 3400, 3220, 2220, 1655 cm⁻¹.

Analogously, the following compounds were prepa-
red:

1- or 2-benzyl-4-cyano-5-amino-1,2,3-triazole

30 1- or 2-(o-fluorobenzyl)-4-cyano-5-amino-1,2,3-triazole

1- or 2-(p-fluorobenzyl)-4-cyano-5-amino-1,2,3-triazole

1- or 2-butyl-4-cyano-5-amino-1,2,3-triazole
1- or 2-isopentyl-4-cyano-5-amino-1,2,3-triazole
1- or 2-(2-methoxyethyl)-4-cyano-5-amino-1,2,3-triazole
1- or 2-heptyl-4-cyano-5-amino-1,2,3-triazole
5 1- or 2-octyl-4-cyano-5-amino-1,2,3-triazole.

Example 5

The preparation of ethoxymethyleneamino heterocycles of formula IV is performed refluxing the respective ortho-aminonitrile with ethyl orthoformate. By way 10 of example, the preparation of 4-cyano-5-(ethoxymethyleneamino)-1-butylypyrazole is reported.

A solution of 4-cyano-5-amino-1-butylypyrazole (20 mmols) in triethyl orthoformate (40 ml) is heated to the reflux temperature under nitrogen atmosphere for 15 8h. The orthoformate excess is evaporated to dryness under vacuum and the residual yellow oil is dissolved in ethyl ether and eluted through silica gel to give the pure compound (87% yield). In many cases, the residue obtained after evaporation of the orthoformate is 20 substantially pure and is used as such in the subsequent step.

IR (nujol): 3140, 2240, 1640 cm⁻¹; ¹H NMR (CDCl₃): 8.4 (s,1H); 7.9 (s,1H); 4.5 (t,2H); 4.3 (q,2H); 1.8 (m,2H); 1.5 (m,2H); 1.4 (t,3H); 0.9 (t,3H).

25 Example 6

A solution of the ethoxymethyleneamino heterocycle (20 mmols) and 2-furoic acid hydrazide (2.5 g, 22 mmols) in 2-methoxyethanol (50 ml) is refluxed for 5-30 10h. After cooling, the solution is evaporated to dryness to obtain a residual oil which is subjected to thermal cyclization in diphenyl ether (50 ml) using a

round-bottom flask fitted with a Dean-Stark apparatus, to remove azeotropically the water formed during the reaction. After varying times (3-5h) the reaction is checked by TLC (2:1 ethyl acetate:petroleum ether) and 5 when the whole starting product has disappeared, the mixture is cooled and added with hexane. The resulting precipitate is filtered and crystallized from the suitable solvent. In some cases, from the solution a viscous oil separates which is decanted and subsequently 10 extracted. The oily residue is then chromatographed on silica gel, eluting with ethyl acetate/petroleum ether mixtures, to give the tricyclic compound VI.

By way of examples, the analytical and spectroscopic 15 characteristics of some compounds prepared by these procedures are reported:

7-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

^1H NMR (DMSO-d₆): 9.6 (s,1H); 8.6 (s,1H); 8.0 (m,1H); 20 7.4 (m,1H); 6.7 (m,1H); 4.5 (t,2H); 1.9 (m,2H); 1.3 (m,2H); 0.9 (t,3H).

8-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

^1H NMR (DMSO-d₆): 9.4 (s,1H); 8.9 (s,1H); 8.0 (m,1H); 25 7.3 (m,1H); 6.2 (m,1H); 4.5 (t,2H); 1.9 (m,2H); 1.3 (m,2H); 0.9 (m,3H). In the 2D-NMR (NOESY) spectrum, the N-CH₂ signal resonating at 4.5 shows cross peaks with the C9-H signal resonating at 8.9.

7-isopentyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine.

30 ^1H NMR (CDCl₃) : 9.1 (s,1H); 8.8 (s,1H); 7.7 (m,1H); 7.3 (m,1H); 6.6 (m,1H); 4.6 (t,2H); 1.18-1.7 (m,3H);

1.0 (d, 6H).

8-isopentyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazo-
lo[1,5-c]pyrimidine.
9.1 (s, 1H); 8.8 (s, 1H); 7.7 (m, 1H); 7.3 (m, 1H); 6.6
5 (m, 1H); 4.6 (t, 2H); 1.9-1.5 (m, 3H); 1.0 (d, 6H).

Following this procedure, the following compounds
were prepared:

7-methyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-
c]pyrimidine

10 8-methyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-
c]pyrimidine

7-(2-chlorophenyl)-2(2-furyl)-pyrazolo[4,3-e]1,2,4-
triazolo[1,5-c]pyrimidine

7-phenylethyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-tria-
zolo[1,5-c]pyrimidine

15 7-tert-butyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-tria-

zolo[1,5-c]pyrimidine

7-(2-cyclopentyl)ethyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-
triazolo[1,5-c]pyrimidine

20 8-benzyl-2(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-
c]pyrimidine

7-benzyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-tria-
zolo[1,5-c]pyrimidine

7-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-
e]1,2,4-triazolo[1,5-c]pyrimidine

25 7-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-
e]1,2,4-triazolo[1,5-c]pyrimidine

7-butyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-tria-
zolo[1,5-c]pyrimidine

30 7-isopentyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-tria-
zolo[1,5-c]pyrimidine

7-(2-methoxy)ethyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
7-heptyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
5 7-octyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
8-benzyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
8-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
10 8-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
8-butyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
15 8-isopentyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
8-hexyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
8-heptyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
20 8-octyl-2(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
9-benzyl-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine
25 9-(2-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine
9-(4-fluorobenzyl)-2(2-furyl)-1,2,3-triazolo[4,5-e]1,2,4-triazolo[1,5-c]pyrimidine

Example 7

30 The compounds of formula VII were prepared according to two methods:

a) by hydrolysis of compounds of formula VI with diluted hydrochloric acid;

b) by thermal cyclization of heterocyclic ortho-amino-nitriles of formula III with 2-furoic acid hydrazide in diphenyl ether at a temperature of 260°C .

5 A) a suspension of the tricyclic compound VI (10 mmols) in 10% HCl (50 ml) is heated to the reflux temperature under stirring for 3h. After cooling, the mixture is alkalinized with concentrated ammonium hydroxide at 0°C and the resulting precipitate is recovered by filtration or extracted with ethyl acetate (3 x 100 ml), dried and evaporated to dryness under vacuum.

10 The residue is purified by either crystallization from the suitable solvents or chromatographed over a 15 silica gel column eluting with ethyl acetate and petroleum ether.

1-t-butyl-4-[3(2-furyl)-1,2,4-triazol-5-yl]-4-amino-pyrazole

1H NMR (CDCl₃): 13.9 (sb,1H); 7.8 (s,1H); 7.7 (s,1H); 20 6.9 (m,1H); 6.6 (s,1H); 6.1 (s,2H); 1.6 (s,9H).

20 B) A suspension of the heterocyclic ortho-amino-nitriles (20 mmols) and 2-furoic acid hydrazide (22 mmols) in diphenyl ether (30 ml) is stirred and heated to reflux (260°C) with a Dean-Stark apparatus until the 25 starting compound has disappeared (TLC, 1-2h). After cooling, the mixture is diluted with petroleum ether and the resulting precipitate is either filtered or separated by decantation and chromatographed on a silica gel column eluting with 2:1 ethyl acetate and petroleum 30 ether.

1-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-

amino-1,2,3-triazole: ^1H NMR (DMSO-d₆): 14.5 (s,1H); 7.8 (s,1H); 7.4-7.1 (m,5H); 6.6 (s,1H); 6.5 (s,2H); 5.5 (s,2H).

Example 8

5 A suspension of the amines of formula VII (10 mmols) in N-methyl-pyrrolidone (40 ml) is added with cyanamide (60 mmols) followed by p-toluenesulfonic acid (15 mmols). The mixture is heated to 160°C with magnetic stirring. After 4h, a second portion of cyanamide (60 mmols) is added and heating is continued overnight. 10 The mixture is then treated with hot water (200 ml) and the precipitated solid is filtered, washed with water and crystallized from ethanol. If no precipitations take place, the solution is extracted with ethyl acetate (4 x 100 ml), the extracts are washed with brine (2 x 50 ml), dried and evaporated to dryness under vacuum. 15 The residue is then chromatographed on a silica gel column eluting with ethyl acetate.

In the following, the analytical and spectroscopic 20 data of some compounds prepared by this procedure are reported:

5-amino-7-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (Compound 292).

M.p. 157-158°C; ^1H NMR (DMSO-d₆) : 8.1 (s,1H); 8.0 (s,2H); 7.9 (m,1H); 7.2 (m,1H); 6.7 (m,1H); 4.2 (t,2H); 1.9 (m,2H); 1.5 (m,2H); 0.9 (t,3H).

5-amino-8-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (Compound 294).

M.p. 183-185°C; ^1H NMR (DMSO-d₆): 8.6 (s,1H); 8.0 (s,1H); 7.6 (s,2H); 7.2 (m,1H); 6.7 (m,1H); 4.2 (t,2H); 1.8 (m,2H); 1.2 (m,2H); 0.9 (t,3H).

5-amino-7-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]-
1,2,4-triazolo[1,5-c]pyrimidine.
M.p. 295-297°C; ^1H NMR (DMSO-d₆): 8.5 (s,2H); 8.0
(s,1H); 7.3 (m,6H); 6.7 (m,1H); 5.7 (s,2H).

5 5-amino-7-o-fluoro-benzyl-2-(2-furyl)-1,2,3-tria-
zolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine
M.p. 310-312°C; ^1H NMR (DMSO-d₆): 8.5 (s,2H); 8.0
(s,1H); 7.3 (m,5H); 6.8 (s,1H); 5.75 (s,2H).

10 5-amino-7-methyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-
triazolo-[1,5-c]pyrimidine; m.p. 210-213°C

5-amino-7-tert-butyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-
triazolo-[1,5-c]pyrimidine; m.p. 238-240°C

5-amino-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-
[1,5-c]pyrimidine; m.p. 248-250°C

15 5-amino-7-(2-hydroxyethyl)-2-(2-furyl)-pyrazolo[4,3-e]-
1,2,4-triazolo-[1,5-c]pyrimidine; m.p. 258-260°C

5-amino-7-phenyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-
triazolo-[1,5-c]pyrimidine; m.p. 295-297°C

5-amino-7-isopentyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-
triazolo-[1,5-c]pyrimidine; m.p. 208-210°C (Compound
20 319).

5-amino-8-isopentyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-
triazolo-[1,5-c]pyrimidine; m.p. 200-203°C (Compound
320).

25 5-amino-7-phenethyl-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-
-triazolo-[1,5-c]pyrimidine; m.p. 225°C (Compound 341).

5-amino-7 β -benzyloxyethyl-2-(2-furyl)-pyrazolo[4,3-e]-
1,2,4-triazolo-[1,5-c]pyrimidine.

5-amino-7-[6-(4-isobutylphenethyl)]-2-(2-furyl)-pyra-
zole[4,3-e]-1,2,4-triazole[1,5-c]pyrimidine m.p. 207-
30 210°C.

Example 9

A suspension of sodium azide (0.23 mole, 15 g) and p-fluorobenzyl chloride (0.15 mole, 18.8 ml) in absolute ethanol (45 ml) is stirred and heated to reflux 5 overnight. After cooling, the suspension is poured into water (200 ml) and from the solution an oil separates which is extracted with ethyl acetate (3 x 100 ml), dried over sodium sulfate and evaporated under vacuum 10 with a bath temperature below 35°C. The residue (20 g, 90%) is used directly in the subsequent step, after IR checking for the presence of the characteristic band of the azido group at 2140 cm⁻¹.

Analogously, starting from β -phenylethanol tosylate in DMF, the 1- β -phenethylazide is obtained.

15

Example 10

p-Fluorobenzylazide (15.1 g, 0.1 mole) and cyanacetamide (10.8 g, 0.13 moles) are added in this order to a suspension of powdered potassium carbonate (57.5 g, 0.42 mole) in dimethylsulfoxide (150 ml).

20

The mixture is stirred at room temperature for 1h. The mixture is poured into 3 l of water and the solid which separates is filtered and washed thoroughly with water to give 22.47 g (96%) of 1-p-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole.

25

M.p.: 198-199°C; ¹H NMR (DMSO-d₆): 7.5-7.1 (m, 6H); 6.4 (s, 2H); 5.4 (s, 2H).

Analogously, 2-fluoro-6-chlorobenzyl-4-carbossamide-5-amino 1,2,3-triazole; m.p. 230-231°C; ¹H-NMR (DMSO-d₆): 5.40 (s, 2H); 6.52 (sb, 2H); 7.12-7.45 (m, 5H).

30

3-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole; m.p. 211-211°C ¹H-NMR (DMSO-d₆): 5.46 (s, 2H); 6.47

(sb, 2H); 7.00-7.52 (m, 6H).

2-fluorobenzyl-4-carboxamido-5-amino 1,2,3-triazole;
m.p. 195-197°C.

1-(β -phenylethyl)-4-carboxamido-5-amino-1,2,3-triazole;

5 m.p. 181-183°C; $^1\text{H-NMR}$ (DMSO-d₆): 3.04 (t, 2H); 4.35
(t, 2H); 6.30 (sb, 2H); 7.20-7.47 (m, 7H) are obtained.

Example 11

A suspension of 1-p-fluorobenzyl-4-carboxamido-5-amino-1,2,3-triazole (23.4 g, 0.1 mole) in DMF (100 ml), magnetically stirred at 0°C, is added with 20.8 ml (0.2 mole) of POCl₃. The solution is stirred for 5' at 0°C, 10' at room temperature and finally 15' at 80°C. After cooling, N HCl (100 ml) is added thereto and the resulting solution is refluxed for 5'; upon cooling 1-p-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole (18.54 g, 90%) precipitates. M.p. 185-186°C; $^1\text{H NMR}$ (DMSO-d₆): 7.3-7.0 (m, 6H); 5.5 (s, 2H); IR (KBr): 3400, 3220, 2220, 1655 cm⁻¹.

Analogously, the following compounds are obtained:

20 2-fluoro-6-chlorobenzyl-4-cyano-5-amino-1,2,3-triazole;
m.p. 181-185°C $^1\text{H-NMR}$ (DMSO-d₆): 5.40 (s, 2H); 7.26-7.50 (m, 5H).

25 3-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole; m.p. 195-197°C $^1\text{H-NMR}$ (DMSO-d₆): 5.44 (s, 2H); 7.00-7.43 (m, 6H).

2-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole; m.p.: 195-197°C.

30 1-(β -phenylethyl)-4-cyano-5-amino-1,2,3-triazole; m.p. 149-150°C $^1\text{H-NMR}$ (DMSO-d₆): 3.04 (t, 2H), 4.36 (t, 2H); 7.03 (sb, 2H); 7.23-7.28 (m, 5H).

Example 12

A suspension of 1-p-fluorobenzyl-4-cyano-5-amino-1,2,3-triazole (20 mmols) and 2-furoic acid hydrazide (22 mmols) in diphenyl ether (30 ml) is stirred and heated to reflux (260°C) with a Dean-Stark apparatus until the starting compound disappears (TLC, 1-2h). After cooling, the mixture is diluted with petroleum ether and the resulting precipitate is either filtered or separated by decantation and chromatographed on a silica gel column eluting with 2:1 ethyl acetate and petroleum ether.

1-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-1,2,3-triazole; m.p. 266-268°C ^1H NMR (DMSO-d₆): 14.5 (s, 1H); 7.8 (s, 1H); 7.4-7.1 (m, 5H); 6.6 (s, 1H); 6.5 (s, 2H); 5.5 (s, 2H). Analogously, the 1-(6-phenylethyl)-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-1,2,3-triazole (50%); m.p. 200-202°C ^1H -NMR (DMSO-d₆): 3.07 (t, 2H); 4.16 (t, 2H); 5.50 (sb, 2H); 6.61 (s, 1H); 6.95 (s, 1H); 7.2-7.4 (m, 5H); 7.78 (s, 1H); 13.8 (sb, 1H) is obtained.

Example 13

A suspension of 1-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-1,2,3-triazole (0.325 g, 1 mmols) in N-methyl-pyrrolidone (4 ml) is added with cyanamide (6 mmols) followed by p-toluenesulfonic acid (1.5 mmols). The mixture is heated at 160°C with magnetic stirring. After 4h, a second portion of cyanamide (6 mmols) is added and heating is continued overnight. The mixture is then treated with hot water (20 ml) and the precipitated solid is filtered, washed with water and crystallized from ethanol. If no precipitations

take place, the solution is extracted with ethyl acetate (4×10 ml), the extracts are washed with brine (2×5 ml), dried and evaporated to dryness under vacuum. The residue is then chromatographed on a silica gel column eluting with ethyl acetate to give 105 mg (30% yield) of 5-amino-7-p-fluoro-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine
5 M.p.: 266-268°C; ^1H NMR (DMSO-d₆) : 8.5 (sb, 2H); 7.95 (s, 1H); 7.4-7.1 (m, 6H); 6.7 (s, 1H); 5.7 (s, 2H)
10 (Compound 340).

Analogously, were obtained:

5-amino-7-o-fluorobenzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine; m.p. 310°C.
5-amino-7-benzyl-2-(2-furyl)-1,2,3-triazolo[5,4-e]-
15 1,2,4-triazolo[1,5-c]pyrimidine; m.p. 295-7°C.
5-amino-7-(2-fluoro-6-chlorobenzyl)-2-(2-furyl)-1,2,3-
triazolo[5,4-e]1,2,4-triazolo[1,5-c]pyrimidine; m.p.
218-220°C; ^1H -NMR (DMSO-d₆): 8.51 (sb, 2H); 7.98 (s,
1H); 7.55-7.28 (m, 4H); 6.77 (m, 1H); 5.73 (s, 2H).
20 5-amino-7-(m-fluorobenzyl)-2-(2-furyl)1,2,3-
triazolo[5,4-e] 1,2,4-triazolo[1,5-c]pyrimidine; m.p.
280-283°C; ^1H -NMR (DMSO-d₆): 8.45 (sb, 2H); 7.98 (s,
1H); 7.4-7.1 (m, 5H); 6.76 (s, 1H); 5.75 (s, 2H).
5-amino-7-(8-phenylethyl)-2-(2-furyl)-1,2,3-
25 triazolo[5,4-e] 1,2,4-triazolo[1,5-c]pyrimidine; m.p.
269-271°C; ^1H -NMR (DMSO-d₆): 8.4 (sb, 2H); 7.98 (s,
1H); 7.3-7.15 (m, 6H); 6.8 (s, 1H); 4.71 (t, 2H); 3.31
(t, 2H) (Compound 376) are obtained.

Example 14

30 A suspension of anhydrous potassium carbonate (30 mmols) in anhydrous DMF (50 ml) is added with 5-amino-

4-cyano-triazole (20 mmols), prepared according to the procedures by Regitz et al. Bull. Soc. Chim. 1975, 1219, and the mixture is heated to a temperature of 80°C for 30 minutes. The suspension is added with p-fluorobenzyl chloride (25 mmols) and heated for 2 h at 80°C. After cooling to room temperature, solvent is evaporated to dryness under vacuum and the resulting residue is taken up into distilled water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts are dried over anhydrous sodium sulfate and evaporated to dryness under vacuum. The resulting residue is chromatographed on a silica gel column with mixtures of ethyl acetate and hexane, to give 2-p-fluorobenzyl-5-amino-4-cyano-2H-1,2,3-triazole (49%).
M.p.: 127-128°C; Anal. C₁₀H₈FN₅ (C, H, N); NMR (DMSO-d₆): 7.4-7.1 (m, 4H); 6.2 (sb, 2H, changeable with D₂O); 5.45 (s, 2H).

Example 15

A suspension of 2-p-fluorobenzyl-5-amino-4-cyano-2H-1,2,3-triazole (20 mmols) and 2-furoic acid hydrazide (22 mmols) in diphenyl ether (30 ml) is stirred and heated to reflux (260°C) with a Dean-Stark apparatus until the starting compound disappears (TLC, 1 hour). After cooling, the mixture is diluted with petroleum ether and the resulting precipitate is either filtered or separated by decantation and chromatographed on a silica gel column eluting with 2:1 ethyl acetate and petroleum ether.

M.p.: 223-225°C; 2-p-fluorobenzyl-4-[3(2-furyl-1,2,4-triazol-5-yl)-5-amino-2H-1,2,3-triazole: ¹H NMR (DMSO-d₆): 14.6 (sb, 1H); 7.86 (s, 1H); 7.4-7.1 (m, 5H); 6.67

(s, 1H); 5.72 (sb, 2H); 5.47 (s, 2H).

Example 16

A suspension of 2-p-fluorobenzyl-4[3(2-furyl)-1,2,4-triazol-5-yl]-5-amino-2H-1,2,3-triazole (0.325 g, 5 mmols) in N-methyl-pyrrolidone (4 ml) is added with cyanamide (6 mmols) followed by p-toluenesulfonic acid (1.5 mmols). The mixture is heated to 160°C with magnetic stirring. After 4 hours, a second portion of cyanamide (6 mmols) is added and heating is continued overnight. The mixture is then treated with hot water (20 ml) and the precipitated solid is filtered, washed with water and crystallized from DMF/H₂O. The crystallization mother solution is extracted with ethyl acetate (4 x 10 ml), the extracts are washed with brine (2 x 5 ml), dried and evaporated to dryness under vacuum. The residue is then chromatographed on a silica gel column eluting with ethyl acetate, to give 105 mg (yield 30%) of 5-amino-8-p-fluorobenzyl-2-(2-furyl)-1,2,3-triazolo-[5,4-e]1,2,4-triazolo[1,5-c] pyrimidine.

M.p.: >285°C; ¹H NMR (DMSO-d₆): 8.05 (sb, 2H); 7.95 (s, 1H); 7.5-7.2 (m, 6H); 6.75 (s, 1H); 5.84 (s, 2H) (Compound 363).

Example 17

A suspension stirred and cooled at 0°C of 80% NaH (1.5 moles) in anhydrous DMF (30 ml) is added with a solution of 4-cyano-5-tosylamino-1,2,3-triazole (1 mmole) in anhydrous DMF (5 ml). The mixture is left to react at room temperature for 1 h, after that p-fluorobenzyl chloride (0.90 mmole) is added. The resulting suspension is heated at 80°C overnight. The mixture is evaporated to dryness and the residue taken up into wa-

ter and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts are dried over sodium sulfate and evaporated to dryness. The oily residue is crystallized from dioxane/water, to give 1-p-fluorobenzyl-5-cyano-4-tosylamino-1-H-1,2,3-triazole in a 56% yield.
5 M.p.: 163-165°C; ^1H NMR (CDCl_3): 7.8-7.7 (m, 2H); 7.26-7.05 (m, 7H); 5.49 (s, 2H); 2.37 (s, 3H).

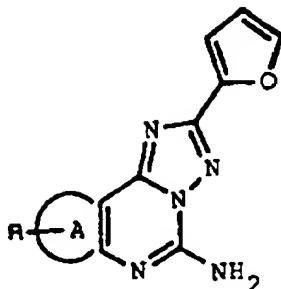
Example 18

10 1-p-Fluorobenzyl-4-amino-5-cyano-triazole is prepared according to the procedures described by Regitz et al. Liebigs Ann. Chem. 1975, 2159-2168, by acid hydrolysis with concentrated sulfuric acid of the compound of example 17, at -15°C.
15 M.p.: 105-108°C; ^1H NMR (DMSO-d_6): 7.44-7.19 (m, 4H); 6.27 (sb, 2H); 5.51 (s, 2H).

CLAIMS

1. Compounds of formula I:

5



10

I

in which:

A is a pyrazole, imidazole or triazole ring;

R is hydrogen; C₁-C₈ alkyl; C₃-C₇ alkenyl, C₃-C₇ alkynyl; C₃-C₇ cycloalkyl; C₁-C₅ alkyl substituted with one or more halogen atoms, hydroxy groups, C₁-C₄ alkoxy, C₃-C₇ cycloalkyl, groups of formula -NR₁R₂, -CONR₁R₂; aryl optionally substituted with halogen atoms, C₁-C₄ alkoxy groups, C₁-C₄ alkyl, nitro, amino, cyano, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, carboxy, carboxyamido; C₇-C₁₀ aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a group of formula -(CH₂)_m-Het, wherein Het is a 5-6 membered aromatic or non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer from 1 to 5;

R₁, R₂, which are the same or different, are hydrogen, C₁-C₅ alkyl, C₇-C₁₀ aralkyl, phenyl, or taken together with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring con-

taining one or more heteroatoms such as N, O, S and n is an integer from 2 to 5, with the proviso that, when A is a pyrazole or imidazole, R is different from fluorobenzyl.

5 2. Compounds according to claim 1, wherein A is a triazole ring.

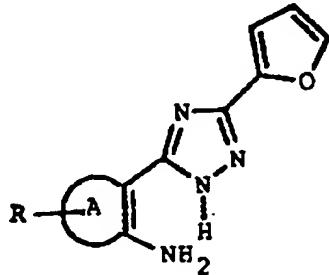
3. Compounds according to claim 1, wherein A is a pyrazole ring.

4. Compounds according to claim 1, wherein A is an 10 imidazole ring.

5. Compounds according to any one of the above claims, wherein R is hydrogen, C₁-C₈ alkyl, aryl or C₇-C₁₀ aralkyl, optionally substituted with halogen atoms.

6. Compounds according to any one of the above claims 15 wherein R is phenethyl in which the phenyl ring may optionally be substituted by one or more substituents selected from chlorine, fluorine atoms, methoxy, nitro, cyano, methyl, trifluoromethyl, difluoromethoxy groups.

7. A process for the preparation of the compounds of 20 formula I which comprises reacting a compound of formula VII



25

VII
wherein R and A are as defined above, with cyanamide.

8. Pharmaceutical compositions containing as the active ingredient one compound of claims 1-6 in admixture 30 with an acceptable carrier.

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/EP 94/02031

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D487/14 A61K31/495 // (C07D487/14, 239:00, 249:00, 249:00),
 (C07D487/14, 231:00, 239:00, 249:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 263 071 (CIBA GEIGY AG) 6 April 1988 Compounds (Ib) see page 7, line 8 - line 9 ---	1-8
Y	EP,A,0 217 748 (CIBA GEIGY AG) 8 April 1987 Compounds (Ic) see page 5, line 64 - line 65 ---	1-8
Y	EUR. J. MED. CHEM. vol. 28 , 1993 pages 569 - 576 GATTA ET AL 'Synthesis of imidazo[1,2-c]pyrazolo[4,3-e]pyrimidines' cited in the application Compounds 13e, 13f, 19e, 19f ---	1-8
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'V' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

1

Date of the actual completion of the international search

Date of mailing of the international search report

20 September 1994

12. 10. 94

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentzaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 94/02031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J.MED.CHEM. vol. 31 , 1988 pages 1014 - 1020 FRANCIS ET AL 'Structure-Activity Profile of a Series of Novel Triazoloquinazoline Adenosine Antagonists.' cited in the application Compound 2a see page 1015 -----	1-8
A	US,A,4 713 383 (FRANCIS) 15 December 1987 see claim 10 -----	1-8

1

INTERNATIONAL SEARCH REPORT

Information on patent family members:

Int'l Application No
PCT/EP 94/02031

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0263071	06-04-88	US-A-	4831013	16-05-89
		AU-B-	612331	11-07-91
		AU-A-	8027187	21-04-88
		CA-A-	1317590	11-05-93
		DE-A-	3781080	17-09-92
		WO-A-	8802370	07-04-88
		ES-T-	2051772	01-07-94
		JP-T-	1500996	06-04-89
-----	-----	-----	-----	-----
EP-A-0217748	08-04-87	JP-A-	62135475	18-06-87
		US-A-	4831013	16-05-89
-----	-----	-----	-----	-----
US-A-4713383	15-12-87	AU-A-	4813285	10-04-86
		EP-A-	0181282	14-05-86
		JP-A-	61165386	26-07-86
-----	-----	-----	-----	-----